General

Guideline Title

Merkel cell carcinoma.

Bibliographic Source(s)

Alberta Provincial Cutaneous Tumour Team. Merkel cell carcinoma. Edmonton (AB): CancerControl Alberta; 2015 Jul. 15 p. (Clinical practice guideline; no. CU-004). [43 references]

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Alberta Cutaneous Tumour Team. Merkel cell carcinoma. Edmonton (Alberta): Alberta Health Services, Cancer Care; 2011 Feb. 12 p. (Clinical practice guideline; no. CU-004). [41 references]

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Merkel cell carcinoma (MCC) is an uncommon cancer and there is a lack of strong evidence to guide practice. Recommendations included are based on available evidence (e.g., poor quality evidence such as case series) and Provincial Tumour Team consensus. Treatment should be individualized based on patients and disease factors.

1. Staging and Work-up
    - Patients should be staged using the American Joint Committee on Cancer staging system for MCC. See Appendix A in the original guideline document (Lemos et al., 2010).
    - History, physical examination, and relevant investigation should guide further treatment.
    - If available, imaging with positron emission tomography/computed tomography (PET/CT) scan is the preferred staging modality to identify distant metastases. CT or magnetic resonance imaging (MRI) can also be used.
2. Treatment

    The treatment of choice for MCC is surgical resection. The tumor is both radiosensitive and chemosensitive, raising the possibility of other strategies in treating this condition. As such patients would benefit from management in multidisciplinary settings.

    Stage I and II

    - Surgery
        - Wide local excision (i.e., intra-operative margins of 1-2 cm if possible, with the final goal being histologically clear pathological

margins) is recommended whenever possible.
    - Mohs micrographic surgery is appropriate as a tissue-sparing technique when the tumour is in a sensitive area such as head and neck area and there are concerns of functional impairment from too radical an excision.
    - Sentinel lymph node biopsy (protocol below) should be performed simultaneously with excision if possible.
    - Standard requirements to be included in the pathology report have been defined by the College of American Pathologists and can be found in the Appendix B in the original guideline document.
- Radiation
    - Local radiation therapy can be considered in patients with MCC who are deemed to be poor operative candidates or who refuse surgery.
    - Adjuvant radiation therapy to the primary site should be considered, regardless of the adequacy of the surgery as determined by clear margins.
    - As an alternative to adjuvant radiation therapy, observation following surgery could be considered in select patients (i.e., small primary, widely excised, no risk factors).
    - Regimen: 45-50 Gy to the surgical bed and the draining regional lymphatics, delivered in 2-2.5 Gy fractions.
    - For patients with unresected tumours or tumours with microscopic evidence of spread beyond resected margins, higher doses of 55 Gy or higher have been recommended.

Stage III

- Surgery
    - Completion lymph node dissection or radiation therapy or both should be given to the nodal basin if the sentinel node (SN) is positive (Cadili & Dabbs, 2010). If deemed inoperable, neoadjuvant radiation therapy should be considered.
    - Standard elements to be included in the pathology report have been defined by the College of American Pathologists and can be found in the Appendix B in the original guideline document.
- Radiation
    - Adjuvant radiation therapy to the primary site and to the regional lymph node basin should be considered.
    - Regimen: 45-50 Gy to the surgical bed and the draining regional lymphatics, delivered in 2-2.5 Gy fractions.
    - For patients with unresected or borderline unresectable tumours, primary radiation therapy with doses of 55 Gy or higher with or without neoadjuvant chemotherapy (with cisplatin or carboplatin and etoposide) can be considered.

Stage IV

- Clinical trial
- Chemotherapy
    - Systemic chemotherapy is the treatment most often used for patients with stage IV disease.
        - Cisplatin or carboplatin
        - Etoposide
        - Topotecan (in older patients)
- Surgery and radiation therapy can be considered, as indicated for metastases.

3. Follow-up
    - Physical exam including complete skin exam and regional lymph node exam
    - Chest x-ray (optional)
    - Imaging performed at the discretion of treating physician (PET/CT, MRI, etc.)
    - Frequency:
        - Year 1: every 3-4 months
        - Year 2: every 4-6 months
        - Years 3+: annual
4. Management of Recurrences
    - Local or regional recurrences: individualize treatment.
    - Disseminated recurrence: treat as per stage IV disease.
    - Patients should be monitored closely for recurrence of locoregional or distant disease. Lymph node or distant metastatic disease has a uniformly grave prognosis; however, there may be a role for chemotherapy in prolonging survival.
    - Given the complex issues in dealing with this aggressive tumor, patients are best served by being cared for in a tertiary care setting with a multidisciplinary approach.
5. Sentinel Lymph Node Biopsy Protocol

   Lymph node deposits of metastatic MCC may be difficult to identify on routine hematoxylin and eosin (H&E)-stained sections. As for melanoma and breast carcinoma, the use of immunohistochemistry has been shown to increase the sensitivity of identifying occult lymph

node metastases (Allen et al., 2001).

Based on recommendations from the College of American Pathologists (2011) and discussions with M.D. Anderson Cancer Center (Prieto, 2010), the following protocol is suggested:

- Bisect sentinel lymph node.
- If initial H&E section is negative, then cut 200 µm into block and repeat H&E stain.
- Perform anti-keratin immunohistochemistry, preferably using an antibody cocktail, including antibody against low-molecular weight keratin (e.g., Cam 5.2).
- If any concerns regarding non-epithelial keratin staining, anti-cytokeratin immunohistochemistry can be performed.

As for melanoma, the number, size, and intra-nodal location of any metastatic deposits of MCC should be documented in the final pathology report (see Appendix B in the original guideline document).

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Merkel cell carcinoma (MCC)

Guideline Category

Diagnosis

Evaluation

Management

Treatment

Clinical Specialty

Dermatology

Oncology

Pathology

Radiation Oncology

Surgery

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To provide recommendations on the management of Merkel cell carcinoma (MCC) in Alberta

Target Population

Adults over the age of 18 years with Merkel cell carcinoma (MCC) of the skin

Note: Different principles may apply to patients with other cutaneous malignancies (i.e., melanoma, basal cell carcinoma, etc.) and those with MCC of non-cutaneous origin or who present with metastatic MCC from an unknown primary. Different principles may apply to pediatric patients as well.

Interventions and Practices Considered

Diagnosis/Evaluation

1. Staging (American Joint Committee on Cancer staging system)
2. History, physical examination, and relevant investigation
3. Positron emission tomography/computed tomography (PET/CT), CT or magnetic resonance imaging (MRI)

Treatment/Management

1. Surgery
    - Wide local excision
    - Mohs micrographic surgery
    - Sentinel lymph node biopsy using protocol (hematoxylin and eosin [H&E]-stained sections, immunohistochemistry)
    - Completion lymph node dissection
    - Pathology report (College of American Pathologists standard requirements)
2. Radiation therapy
    - Primary site and regional lymph node basin
    - Local and adjuvant
    - Consideration of observation as alternative to adjuvant radiation
    - Regimen: 45-50 Gy or higher
3. Systemic chemotherapy (cisplatin, carboplatin etoposide, topotecan)
4. Clinical trial
5. Follow-up (physical exam, chest x-ray, imaging)
6. Management of recurrences

Major Outcomes Considered

- Sensitivity and specificity of diagnostic tests
- Survival rates (5-year, overall, disease-free, disease-specific, progression-free)
- Recurrence/relapse rate
- Regional lymph node involvement
- Rate of regional or distant metastasis

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Research Questions

Specific research questions to be addressed by the guideline document were formulated by the guideline lead(s) and Knowledge Management (KM) Specialist using the PICO question format (Patient or Population, Intervention, Comparisons, Outcomes).

Guideline Questions

- What is the widely accepted staging classification for Merkel cell carcinoma (MCC)?
- What is the most appropriate treatment for MCC Stage I-IV?
- What are the management strategies for recurrence of MCC?
- How should a patient with MCC be followed?

Search Strategy

The MEDLINE (search dates: 2011 to 2014-12-10), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane, American Society of Clinical Oncology (ASCO) abstracts and proceedings (search dates: 2011 to 2014-12-10) and PubMed (search dates: 2013 to 2014-12-15), databases were searched for practice guidelines, systematic reviews, and clinical trials relevant to the topic. In addition, the National Guideline Clearinghouse (NGC) and individual guideline organizations were searched (search dates: 2011 to 2014-12-10) for relevant practice guidelines. The search included retrospective or prospective studies with >10 patients with MCC, outcomes (response, control, survival) reported by treatment type.

Search terms included 'Merkel cell carcinoma' and 'skin or cutaneous'. Non-English publications were excluded, as well as publications that included less than ten patients with MCC. The original search included publications from the year 1966 and onward with subsequent updates covering publications from the date of the last search through the date on which the update was conducted. The latest update searched MEDLINE and PubMed databases (January 2011 through December 2014) and retrieved 512 articles. An additional eight studies were identified through hand searching and the ASCO abstracts database.

Number of Source Documents

A total of 28 relevant articles were identified. In addition, two clinical practice guidelines were identified from the National Comprehensive Cancer Network and the French Society of Dermatology.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Expert Consensus (Committee)

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Cutaneous Tumour Team and a

Knowledge Management (KM) Specialist from the Guideline Resource Unit (GURU). A detailed description of the methodology followed during the guideline development process can be found in the GURU Handbook (see the "Availability of Companion Documents" field).

Evidence Tables

Evidence tables containing the first author, year of publication, patient group/stage of disease, methodology, and main outcomes of interest are assembled using the studies identified in the literature search. Existing guidelines on the topic are assessed by the KM Specialist using portions of the Appraisal of Guidelines Research and Evaluation (AGREE) II instrument (http://www.agreetrust.org/) and those meeting the minimum requirements are included in the evidence document. Due to limited resources, GURU does not regularly employ the use of multiple reviewers to rank the level of evidence; rather, the methodology portion of the evidence table contains the pertinent information required for the reader to judge for himself the quality of the studies.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Development and Revision History

This guideline was reviewed and endorsed by the Alberta Provincial Cutaneous Tumour Team. Members of the Alberta Provincial Cutaneous Tumour Team include surgeons, dermatologists, dermatopathologists, medical oncologists, radiation oncologists, nurses, and researchers. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Cutaneous Tumour Team and a Knowledge Management (KM) Specialist from the Guideline Resource Unit (GURU). A detailed description of the methodology followed during the guideline development process can be found in the GURU Handbook (see the "Availability of Companion Documents" field).

This guideline was originally developed in May 2008. This guideline was revised in November 2009, May 2010, March 2011, and most recently in July 2015.

Formulating Recommendations

The working group members formulate the guideline recommendations based on the evidence synthesized by the KM Specialist during the planning process, blended with expert clinical interpretation of the evidence. As detailed in the GURU Handbook, the working group members may decide to adopt the recommendations of another institution without any revisions, adapt the recommendations of another institution or institutions to better reflect local practices, or develop their own set of recommendations by adapting some, but not all, recommendations from different guidelines.

The degree to which a recommendation is based on expert opinion of the working group and/or the Provincial Tumour Team members is explicitly stated in the guideline recommendations. Similar to the American Society of Clinical Oncology (ASCO) methodology for formulating guideline recommendations, the GURU does not use formal rating schemes for describing the strength of the recommendations, but rather describes, in conventional and explicit language, the type and quality of the research and existing guidelines that were taken into consideration when formulating the recommendations.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published analyses were not reviewed.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

This guideline was reviewed and endorsed by the Alberta Provincial Cutaneous Tumour Team.

Guideline Review and Approval

When the draft guideline document has been completed, revised, and reviewed by the Knowledge Management (KM) Specialist and the working group members, it is sent to all members of the Provincial Tumour Team for review and comment. This step ensures that those intended to use the guideline have the opportunity to review the document and identify potential difficulties for implementation before the guideline is finalized. Depending on the size of the document, and the number of people it is sent to for review, a deadline of one to two weeks will usually be given to submit any feedback. Ideally, this review will occur prior to the annual Provincial Tumour Team meeting, and a discussion of the proposed edits will take place at the meeting. The working group members will then make final revisions to the document based on the received feedback, as appropriate. Once the guideline is finalized, it is officially endorsed by the Provincial Tumour Team Lead and the Director of Provincial Clinical Teams.

Evidence Supporting the Recommendations

References Supporting the Recommendations

Allen PJ, Busam K, Hill AD, Stojadinovic A, Coit DG. Immunohistochemical analysis of sentinel lymph nodes from patients with Merkel cell carcinoma. Cancer. 2001 Sep 15;92(6):1650-5. PubMed

Cadili A, Dabbs K. Predictors of sentinel lymph node metastasis in melanoma. Can J Surg. 2010 Feb;53(1):32-6. PubMed

College of American Pathologists. Protocol for the examination of specimens from patients with Merkel cell carcinoma of the skin. Version 3.0.1.0. [internet]. 2011

Lemos BD, Storer BE, Iyer JG, Phillips JL, Bichakjian CK, Fang LC, Johnson TM, Liegeois-Kwon NJ, Otley CC, Paulson KG, Ross MI, Yu SS, Zeitouni NC, Byrd DR, Sondak VK, Gershenwald JE, Sober AJ, Nghiem P. Pathologic nodal evaluation improves prognostic accuracy in Merkel cell carcinoma: analysis of 5823 cases as the basis of the first consensus staging system. J Am Acad Dermatol. 2010 Nov;63(5):751-61. PubMed

Prieto V. (Department of Pathology, University of Texas MD Anderson Cancer Center). Personal communication. 2010 Apr 4.

Type of Evidence Supporting the Recommendations

Recommendations are based on available evidence (e.g., poor quality evidence such as case series) and Provincial Tumour Team consensus.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate management of Merkel cell carcinoma (MCC)

Potential Harms

Some patients with Merkel cell carcinoma (MCC) do respond to chemotherapy, but toxicity must be weighed against the benefits.

Qualifying Statements

Qualifying Statements

The recommendations contained in this guideline are a consensus of the Alberta Provincial Cutaneous Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

Implementation of the Guideline

Description of Implementation Strategy

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services Web site.
- Send an electronic notification of the new guideline to all members of CancerControl Alberta.

Implementation Tools

Chart Documentation/Checklists/Forms

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

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Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2015 Jul

Guideline Developer(s)

CancerControl Alberta - State/Local Government Agency [Non-U.S.]

Source(s) of Funding

CancerControl Alberta

Guideline Committee

Alberta Provincial Cutaneous Tumour Team

Composition of Group That Authored the Guideline

Members of the Alberta Provincial Cutaneous Tumour Team include surgeons, dermatologists, dermatopathologists, medical oncologists, radiation oncologists, nurses, and researchers.

Financial Disclosures/Conflicts of Interest

Participation of members of the Alberta Provincial Cutaneous Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Cutaneous Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However, the developers of this guideline are satisfied it was developed in an unbiased manner.

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Alberta Cutaneous Tumour Team. Merkel cell carcinoma. Edmonton (Alberta): Alberta Health Services, Cancer Care; 2011 Feb. 12 p. (Clinical practice guideline; no. CU-004). [41 references]

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the Alberta Health Services Web site .

Availability of Companion Documents

The following is available:

- Guideline utilization resource unit handbook. Version 2. Edmonton (AB): CancerControl Alberta; 2013 Jan. 5 p. Available from the Alberta

Health Services Web site .

In addition, the American Joint Committee on Cancer (AJCC) (7th Edition) anatomic stage/prognostic groups for Merkel cell carcinoma and the College of American Pathologists' checklist for reporting elements for Merkel cell carcinoma following incisional biopsy, excision, re-excision, or lymphadenectomy are available in the appendices of the original guideline document .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on December 24, 2012. The information was verified by the guideline developer on February 13, 2013. This summary was updated by ECRI Institute on March 14, 2016. The updated information was verified by the guideline developer on April 4, 2016.

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